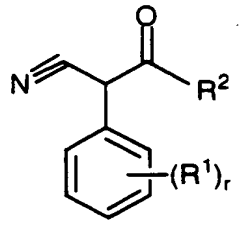
CLAIMS

What is claimed is:

1. A process for the preparation of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt form thereof;
wherein:
r is an integer from 0 to 4;
R^1 is independently selected at each occurrence from the group consisting of:
H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{1c}R^{1d}$, $-OR^{1e}$, and $-SR^{1e}$;
R^{1c} and R^{1d} are independently selected at each occurrence from the group consisting of:
H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl;
alternatively, R^{1c} and R^{1d} are taken together to form a heterocyclic ring selected from the group consisting of:
piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C_1-C_4 alkyl groups;
R^{1e} is independently selected at each occurrence from the group consisting of:
H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;
R^2 is selected from the group consisting of:
H, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkyl substituted with 0-5 R^{2a};

R^{2a} is independently selected at each occurrence from the group consisting of:

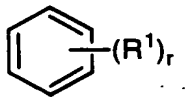
H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl, $-OR^{2e}$, and $-SR^{2e}$; and

R^{2e} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

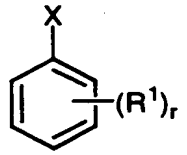
the process comprising the steps of:

(1) contacting a compound of formula (II):



(II)

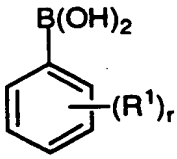
with a halogenating agent to form a compound of formula (III):



(III);

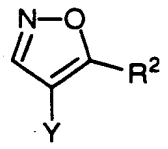
wherein X is a halogen derived from the halogenating agent;

(2) contacting the compound of formula (III) with a strong base followed by addition of an alkylborate to form a compound of formula (IV):



(IV);

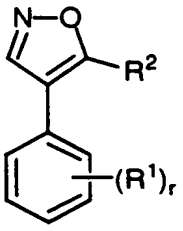
(3) contacting the compound of formula (IV) with a compound of formula (V):



(V)

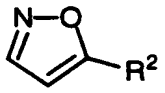
wherein Y is a second halogen;

in the presence of a catalyst and a weak base to form a compound of formula (VI):



(VI); and

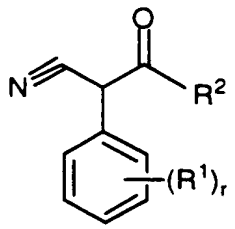
(4) contacting the compound of formula (VI) with an isomerization base to form a compound of formula (I), or a pharmaceutically acceptable salt form thereof;
wherein the compound of formula (V) is prepared by contacting a compound of formula (VII):



(VII)

with a second halogenating agent to give a compound of formula (V).

2. A process for the preparation of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt form thereof;

wherein:

r is an integer from 0 to 4;

R^1 is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{1c}R^{1d}$, $-OR^{1e}$, and $-SR^{1e}$;

R^{1c} and R^{1d} are independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl;

alternatively, R^{1c} and R^{1d} are taken together to form a heterocyclic ring selected from the group consisting of:

piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^{1e} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

R^2 is selected from the group consisting of:

H, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkyl substituted with 0-5 R^{2a};

R^{2a} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl, $-OR^{2e}$, and $-SR^{2e}$; and

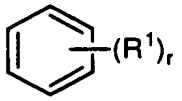
R^{2e} is independently selected at each occurrence from the

group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

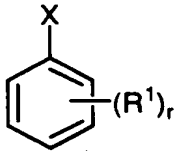
the process comprising the steps of:

(1) contacting a compound of formula (II):



(II)

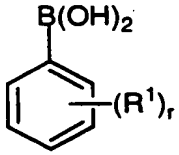
with a halogenating agent to form a compound of formula (III):



(III);

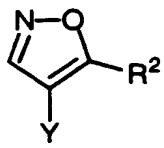
wherein X is a halogen derived from the halogenating agent;

(2) contacting the compound of formula (III) with a strong base followed by addition of an alkylborate to form a compound of formula (IV):



(IV);

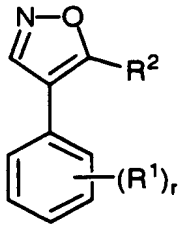
(3) contacting the compound of formula (IV) with a compound of formula (V):



(V)

wherein Y is a second halogen;

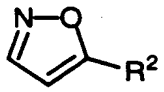
in the presence of a catalyst and a weak base to form a compound of formula (VI):



(VI); and

(4) contacting the compound of formula (VI) with an isomerization base to form a compound of formula (I), or a pharmaceutically acceptable salt form thereof;

wherein the compound of formula (V) is prepared by contacting a compound of formula (VII):

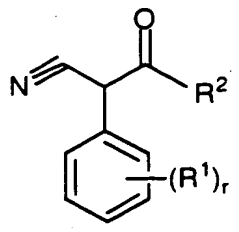


(VII)

with a halogenating agent in an organic acid to form a compound of formula (V).

3. The process of Claim 2, wherein R^2 is methyl, the halogenating agent is N-iodosuccinimide, and the organic acid is triflouroacetic acid.

4. A process for the preparation of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt form thereof;

wherein:

r is an integer from 0 to 4;

R^1 is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{1c}R^{1d}$, $-OR^{1e}$, and $-SR^{1e}$;

R^{1c} and R^{1d} are independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl;

alternatively, R^{1c} and R^{1d} are taken together to form a heterocyclic ring selected from the group consisting of:

piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^{1e} is selected from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

R^2 is selected from the group consisting of:

H, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkyl substituted with 0-5 R^{2a};

R^{2a} is independently selected at each occurrence from the group consisting of:

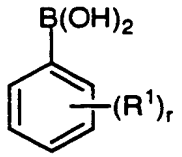
H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl, $-OR^{2e}$, and $-SR^{2e}$; and

R^{2e} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

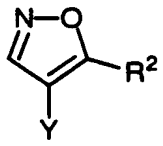
the process comprising the steps of:

(1) contacting a compound of formula (IV):



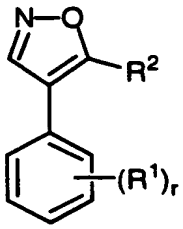
(IV)

with a compound of formula (V):



(V)

wherein Y is a halogen;
in the presence of a catalyst and a weak base to give a compound of formula (VI):



(VI); and

(2) contacting the compound of formula (VI) with an isomerization base to give a compound of formula (I), or a pharmaceutically acceptable salt form thereof.

5. The process of Claim 4, wherein:
r is an integer from 0-3;

Y is iodine;
R^1 is independently selected at each occurrence from the group consisting of:
H, methyl and methoxy; and
R^2 is methyl.

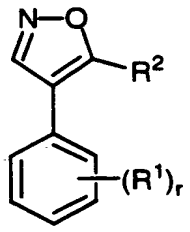
6. The process of Claim 4, wherein:
in step 1, the weak base is sodium bicarbonate or a phosphate buffer with pH of about 7 to about 10,

the catalyst is tetrakis(triphenylphosphine)palladium(0) or [1,1'-Bis(diphenylphosphino)ferrocene] palladium (II) chloride; and

in step 2, the isomerization base is selected from the group consisting of:
lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, lithium tert-butoxide, sodium tert-butoxide, and potassium tert-butoxide.

7. The process of Claim 4, wherein:
the weak base is sodium bicarbonate, the catalyst is [1,1'-Bis(diphenylphosphino)ferrocene] palladium (II) chloride, and the isomerization base is sodium methoxide.

8. A process for the preparation of a compound of formula (VI):



(VI)

or a pharmaceutically acceptable salt form thereof;
wherein:

r is an integer from 0 to 4;

R^1 is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{1c}R^{1d}$, $-OR^{1e}$, and $-SR^{1e}$;

R^{1c} and R^{1d} are independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl;

alternatively, R^{1c} and R^{1d} are taken together to form a heterocyclic ring selected from the group consisting of:

piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^{1e} is selected from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

R^2 is selected from the group consisting of:

H, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkyl substituted with 0-5 R^{2a};

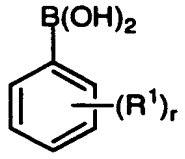
R^{2a} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl, $-OR^{2e}$, and $-SR^{2e}$; and

R^{2e} is independently selected at each occurrence from the group consisting of:

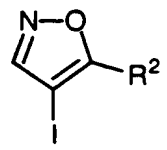
H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

the process comprising contacting a compound of formula (IV):



(IV)

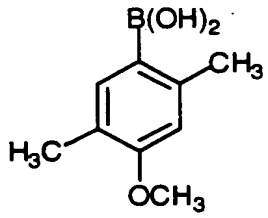
with a compound of formula (V):



(V)

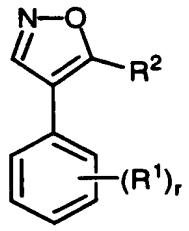
in the presence of [1,1'-Bis(diphenylphosphino)ferrocene] palladium (II) chloride, sodium bicarbonate and a suitable solvent to give a compound of formula (VI).

9. The process of Claim 8, wherein:
R^2 is methyl;
the suitable solvent is tert-butyl methyl ether; and
the compound of formula (IV) is:



(IV).

10. A compound of formula (VI):



(VI);

wherein:
r is an integer from 0 to 4;
R^1 is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{1c}R^{1d}$, $-OR^{1e}$, and $-SR^{1e}$;

R^{1c} and R^{1d} are independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl;

alternatively, R^{1c} and R^{1d} are taken together to form a heterocyclic ring selected from the group consisting of:

piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^{1e} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

R^2 is selected from the group consisting of:

H, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkyl substituted with 0-5 R^{2a};

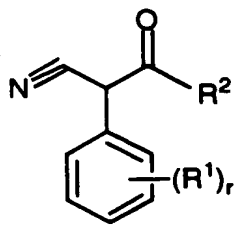
R^{2a} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl, $-OR^{2e}$, and $-SR^{2e}$; and

R^{2e} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl.

11. A compound of formula (I):



(I)

wherein:

r is an integer from 0 to 4;

R^1 is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, $-NR^{1c}R^{1d}$, $-OR^{1e}$, and $-SR^{1e}$;

R^{1c} and R^{1d} are independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl and C_4-C_{12} cycloalkylalkyl;

alternatively, R^{1c} and R^{1d} are taken together to form a heterocyclic ring selected from the group consisting of:

piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine and thiomorpholine, each heterocyclic ring optionally substituted with 1-3 C_1-C_4 alkyl groups;

R^{1e} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl;

R^2 is selected from the group consisting of:

H, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_3-C_6 cycloalkyl, C_4-C_{10} cycloalkylalkyl, C_1-C_4 hydroxyalkyl, C_1-C_4 haloalkyl, and C_1-C_4 alkyl substituted with 0-5 R^{2a};

R^{2a} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_3-C_6 cycloalkyl, C_4-C_{12} cycloalkylalkyl, halo, CN, C_1-C_4 haloalkyl, $-OR^{2e}$, and $-SR^{2e}$; and

R^{2e} is independently selected at each occurrence from the group consisting of:

H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, and C_4-C_6 cycloalkylalkyl.